PATENT APPLICATION

SYSTEMS AND METHODS FOR MODULATING AUTONOMIC FUNCTION

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SYSTEMS AND METHODS FOR MODULATING AUTONOMIC FUNCTION

CROSS REFERENCE TO RELATED APPLICATIONS

5   [0001] This application is a continuation in part application of U.S. Application No. 10/660,462, filed September 11, 2003, which is a continuation in part application of U.S. Patent Application No. 10/460,558, filed June 11, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/426,161, filed April 28, 2003, the complete disclosures of which are herein incorporated by reference.

10 [0002]   This application is also a continuation in part application of U.S. Patent Application No. 10/401,493, filed March 28, 2003, which is a continuation in part application of U.S. Patent Application Serial No. 10/224,263, filed August 19, 2002, which is a continuation in part application of U.S. Patent Application Serial No. 10/119,203, filed April 8, 2002, which is a continuation in part application of U.S. Patent Application Serial No. 09/854,238, filed

15 May 11, 2001, which is a continuation in part application of U.S. Patent Application Serial No. 09/546,252, filed April 10, 2000, which is a continuation of U.S. Patent Application No. 08/950,702, filed October 15, 1997 (now U.S. Patent No. 6,062,219), which is a continuation-in-part application of U.S. Patent Application Serial No. 08/403,009, filed March 10, 1995 (now U.S. Patent No. 5,692,498), which is a continuation-in-part application of U.S. Patent

20 Application Serial No. 08/149,204, filed November 9, 1993 (now U.S. Patent No. 5,551,420), the disclosures of which are herein incorporated by reference.

BACKGROUND OF THE INVENTION

[0003]   This invention relates generally to the field of intrathoracic pressures. More specifically, the invention relates to a variety of conditions that may be treated by

25 manipulating intrathoracic pressures.

[0004]   A widespread need exists for treating ailments associated with poor blood flow and low blood pressure. For instance, poor blow flow and low blood pressure may be linked to conditions such as poor wound healing, strokes, heart failure, anxiety disorders, sleep disorders and the like. Hence, this invention is related to the intentional manipulation of

30 internal body pressures in order to treat these and a variety of other conditions.

BRIEF SUMMARY OF THE INVENTION

[0005] In one embodiment, the invention provides a method for modulating a person's autonomic function. According to the method, a valve system is interfaced to the person's airway. The valve system is configured to decrease or prevent respiratory gas flow to the person's lungs during at least a portion of an inhalation event. The person is permitted to inhale and exhale through the valve system. During inhalation the valve system functions to produce a vacuum within the thorax to transiently decrease intrathoracic pressure and thereby modulate the person's autonomic function. More specifically, by lowering the intrathoracic pressure, the person experiences enhanced venous return of blood to the heart, and this causes an increase in cardiac output, an increase in blood pressure, and increase in blood flow to the brain, a decrease in intracranial pressure, and an autonomic nervous system-modulated decrease in sympathetic tone resulting in a decrease in peripheral arterial resistance.

[0006] For such a treatment, the valve system may include a pressure responsive inflow valve having an actuating pressure of the valve in the range from about -2 cm H2O to about -30 cm H2O, and more preferably from about -3 cm H2O to about -12 cm H2O for flow rates of about 30 to about 50 liters per minute. In such cases, inhalation the valve system may function to decrease the person's heart rate and peripheral vascular tone. Also, as blood flow increases back to the right heart of the person, vital organ perfusion and function is enhanced. Another advantage is that heart rate variability may also be increased and sympathetic tone may be decreased. Such techniques may also be used to reduce the person's anxiety level and to treat shock secondary to hypovolemia, sepsis and heart failure. In some cases, the techniques may be used to treat sleep disorders, such as sleep apnea, and to treat states of hypo-perfusion, such as wound healing, stroke and diseases where blood flow is compromised, including coronary artery disease. In one particular treatment, the invention may be used to improve blood flow to the muscles and brain, thereby reducing heart rate and enhancing recovery from physical exertion. For example, as intrathoracic pressures are reduced, more heart filling and improved blood circulation results. The nervous system responds by reducing the heart rate and overall the body recovers more quickly. Such techniques may also be used before a person begins to exercise.

[0007] The invention also includes a device for modulating a person's autonomic function. The device comprises a housing having an opening that is adapted to be interfaced with the person's airway, and a valve system that is operable to regulate respiratory gas flow through

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the housing and into the person's lungs due to inhalation. The valve system is employed to assist in manipulating intrathoracic pressures during inhalation to produce a vacuum within the thorax to transiently decrease intrathoracic pressure and thereby modulate the person's autonomic function. The valve system may also be configured to permit respiratory gases to flow to the person's lungs when the negative intrathoracic pressure reaches a pressure in the range from about -2 cm H2O to about -30 cm H2O, and more preferably range from about -3 cm H2O to about -12 cm H2O in order to modulate the person's autonomic function.

[0008] In another embodiment, the invention provides a device for decreasing intracranial or intraocular pressures. The device comprises a housing having an inlet opening and an outlet opening that is adapted to be interfaced with a person's airway. The device further includes a valve system that is operable to regulate respiratory gas flows through the housing and into the person's lungs during spontaneous or artificial inspiration. The valve system assists in lowering intrathoracic pressures during inspiration to continuously or intermittently lower pressures in the venous blood vessels that transport blood out of the head to thereby reduce intracranial or intraocular pressures.

[0009] Such a device may also be used to facilitate movement of cerebral spinal fluid. In so doing, intracranial pressures may be further reduced. Such a device may therefore be used to treat those suffering from head trauma associated with elevated intracranial pressures as well as those suffering from heart conditions that increase intracranial pressures.

[0010] In one aspect, the valve system is configured to open to permit respiratory gasses to freely flow to the person's lungs when the negative intrathoracic pressure reaches a pressure in the range from about -2 cmH2O to about -20 cmH2O in order to reduce intracranial or intraocular pressures. In this way, the negative intrathoracic pressure is lowered until a threshold pressure is reached, at which time the valve opens. The cycle may be repeated continuously or periodically to repetitively lower intrathoracic pressures.

[0011] The device may also include means for causing the person to artificially inspire through the valve system. For example, the device may utilize an electrode, an iron lung cuirass device, a chest lifting device, a ventilator or the like.

[0012] In another embodiment, the device may comprise a means to reduce intrathoracic pressure by applying a vacuum within the airway. The vacuum may be adjusted in terms of frequency, amplitude, and duration. This results in a decrease in intracranial pressure in

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proportion to the degree of vacuum applied. Hence, intracranial pressures may be reduced simply by manipulating airway pressures to reduce intrathoracic pressures.

[0013]   The device may further include a mechanism for varying the level of impedance of the valve system. This may be used in combination with at least one physiological sensor that is configured to monitor at least one physiological parameter of the person. In this way, the mechanism for varying the level of impedance may be configured to receive signals from the sensor and to vary the level of impedance of the valve system based on the signals. Examples of sensors that may be used include those that measure respiratory rate, intrathoracic pressure, intratracheal pressure, blood pressure, heart rate, end tidal CO_2, oxygen level, intracranial perfusion, and intracranial pressure.

[0014]   In one aspect, a coupling mechanism may be used to couple the valve system to the person's airway. Examples of coupling mechanisms include a mouthpiece, an endotracheal tube, and a face mask.

[0015]   A wide variety of valve systems may be used to repetitively decrease the person's intrathoracic pressure. For example, valve systems that may be used include those having spring-biased devices, those having automated, electronic or mechanical systems to occlude and open a valve lumen, duck bill valves, ball valves, other pressure sensitive valve systems capable of opening a closing when subjected to low pressure differentials triggered either by spontaneous breathing and/or external systems to manipulate intrathoracic pressures (such as ventilators, phrenic nerve stimulators, iron lungs, and the like).

[0016]   In another embodiment, the invention provides a method for decreasing intracranial or intraocular pressures. According to the method, a valve system is coupled to a person's airway and is configured to at least periodically reduce or prevent respiratory gases from flowing to the person's lungs. With the valve system coupled to the airway, the person's negative intrathoracic pressure is repetitively decreased to in turn repetitively lower pressures in the venous blood vessels that transport blood out of the head. In so doing, intracranial and intraocular pressures are reduced. Such a method also facilitates movement of cerebral spinal fluid. In so doing, intracranial pressures are further reduced. As such, this method may also be used to treat a person suffering from head trauma that is associated with elevated intracranial pressures as well as those suffering from heart conditions that increase intracranial pressures, such as atrial fibrillation and heart failure.

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[0017] The person's negative intrathoracic pressure may be repetitively decreased as the person repeatedly inspires through the valve system. This may be done by the person's own efforts (referred to as spontaneous breathing), or by artificially causing the person to repeatedly inspire through the valve system. For example, the person may be caused to artificially inspire by repeatedly stimulating the phrenic nerve, by manipulating the chest with an iron lung cuirass device, by generating negative pressures within the thorax using a ventilator, by applying a high frequency ventilator that supplies oscillations at a rate of about 200 to about 2000 per minute, or the like.

[0018] In another aspect, the level of impedance of the valve system may be fixed or variable. If variable, at least one physiological parameters of the person may be measured, and the impedance level may be varied based on the measured parameters.

[0019] To couple the valve system to the airway, a variety of techniques may be used, such as by using a mouthpiece, an endotracheal tube, a face mask or the like. Further, the respiratory gases may be prevented from entering the lungs through the valve system until a negative intrathoracic pressure in the range from about 0 cmH2O to about -25 cmH2O is achieved, at which time the valve system permits respiratory gases to flow to the lungs.

[0020] In another embodiment, the invention provides a method for treating a person suffering from head trauma associated with elevated intracranial pressures. According to the method, a positive pressure breath is delivered to the person. Following the positive pressure breath, respiratory gases are extracted from the person's airway to create an intrathoracic vacuum. In turn, this lowers pressures in the venous blood vessels that transport blood out of the head to thereby reduce intracranial pressures. The steps of delivering positive pressure breaths and extracting respiratory gases are repeated to continue the treatment.

[0021] In one aspect, the delivery of the positive pressure breaths and the extraction of gases are performed using a mechanical ventilator. The respiratory gases may be extracted with a constant extraction or a pulsed extraction.

[0022] In a further aspect, the breath may be delivered for a time in the range for about 250 milliseconds to about 2 seconds. Also, the breath may be delivered at a rate in the range from about 0.1 liters per second to about 5 liters per second. In another aspect, the vacuum may be maintained at a pressure in the level from about 0 mmHg to about -50 mmHg. The vacuum may be maintained with a negative flow or without any flow. The time that the positive

pressure breath is supplied relative to the time in which respiratory gases are extracted may be in the range from about 0.5 to about 0.1.

[0023]   A variety of equipment may be used to extract the respiratory gases including mechanical ventilators, phrenic nerve stimulators, ventilator bags, iron lung cuirass devices and the like. In some cases, a threshold valve may also be coupled to the person's airway. The threshold valve may be configured to open when an adult's negative intrathoracic pressure exceeds about -5 cmH2O. For pediatric cases, the valve may open when the pressure exceeds about -2 cmH2O to about -5 cmH2O. In this way, when the person inhales, the negative intrathoracic pressure may be lowered.

[0024]   A variety of schemes may be used to deliver and extract respiratory gases. For example, respiratory gases may be extracted to achieve a pressure of about -5 mmHg to about -10 mmHg and then kept generally constant until the next positive pressure breath. As another example, the positive breath may be slowly delivered and the intrathoracic pressure may be rapidly lowered to a pressure of about -10 mmHg to about -20 mmHg and then gradually reduced towards about 0 mmHg. As a further example, the intrathoracic pressure may be slowly lowered to a pressure of about -20 mm Hg.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025]   Fig. 1 is a flow chart illustrating one method for reducing intracranial and intraocular pressures according to the invention.

[0026]   Fig. 2 is a perspective view of one embodiment of a facial mask and a valve system that may be used to reduce intracranial and intraocular pressures according to the invention.

[0027]   Fig. 3 is a perspective view of the valve system of Fig. 2.

[0028]   Fig. 4 is a cross sectional side view of the valve system of Fig. 3.

[0029]   Fig. 5 is an exploded view of the valve system of Fig. 3.

[0030]   Fig. 6 is a schematic diagram of a system for reducing intracranial and intraocular pressures according to the invention.

[0031]   Fig. 7 is a series of graphs illustrating the lowering of intracranial pressures in an animal study.

[0032]   Fig. 8 is a series of graphs illustrating the lowering of intracranial pressures in another animal study.

[0033]   Fig. 9A is a schematic diagram of a person's brain under normal conditions.

[0034]   Fig. 9B illustrates the brain of Fig. 9A after increased swelling.

[0035]   Fig. 10 shows three graphs illustrating the effect of lowering intrathoracic pressure on intracranial pressure and right atrial pressure.

[0036]   Fig. 11 is a flow chart illustrating another method for reducing intracranial and intraocular pressures according to the invention.

[0037]   Figs. 12A-12C show three graphs illustrating patterns for delivering a positive pressure breath and extracting respiratory gases according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0038]   In one aspect, the invention provides devices and techniques for lowering intracranial and intraocular pressures. Such devices and techniques may be particularly helpful with patients who have suffered a traumatic brain injury. One way to lower such pressures is by using a valve system that is coupled to a person's airway and that is used to lower intrathoracic pressures. In so doing, the valve systems may be used to accelerate the removal of venous blood from the brain, thereby decreasing intracranial and intraocular pressures. Other techniques may be used as well, such as by creating a vacuum intermittently within the thorax. By reducing intracranial pressures, movement of cerebral spinal fluid is also enhanced. In so doing, intracranial pressures are further reduced thereby providing further treatment for those suffering from head trauma. In some cases, the valve systems may also be used to treat the brain function in a person suffering from a heart condition (atrial fibrillation, heart failure, cardiac tamponade, and the like) that results in elevated intracranial pressures. Such heart conditions may include, for example, atrial fibrillation or heart failure. By reducing intracranial pressures, cerebral spinal fluid movement and translocation is increased to help improve brain function.

[0039]   Intracranial pressures are regulated by the amount the cerebral perfusion pressure, which is determined by the arterial blood pressure to the head, the pressures within the skull, and the pressures within the venous system that drains blood flow from the brain. The devices and methods of the invention may be used to enhance the egress of venous blood out

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of the brain, thereby lowering intracranial pressures. To do so, the devices and methods may be used to augment the intrathoracic vacuum effect each time a patient inhales (or in the case of a non-breathing patient, each time the pressure within the chest is manipulated to fall below atmospheric pressure), thereby lowering the pressures in the thorax and in the venous blood vessels that transport blood out of the brain. The vacuum effect is transduced back into the brain, and as a result, intracranial pressures are lowered with each inspiratory effort. This in turn causes more venous blood to flow out of the head than would otherwise be possible, resulting in lower intracranial pressures and lower intraocular pressures.

[0040] Similar techniques may also be used to alter autonomic nervous system function and result in at least a transient decrease in heart rate and peripheral arterial resistance. For instance, because of lowered intracranial pressures, an autonomic nervous system-modulated decrease in sympathetic tone may result. This may lead to a decrease in peripheral arterial resistance. Other results that may be achieved using such techniques include an increased heart rate variability and a reduction in the person's anxiety level. Also, the techniques may be used to treat shock secondary to hypovolemia, sepsis and heart failure. In some cases, the techniques may be used to treat sleep disorders, such as sleep apnea, and to treat states of hypo-perfusion, such as wound healing, stroke and diseases where blood flow is compromised, including coronary artery disease. In one particular treatment, the invention may be used to improve blood flow to the muscles and brain, thereby reducing heart rate and enhancing recovery from physical exertion. The reduced intrathoracic pressures may result in increased heart filling and circulation. As a result, the nervous system may reduce heart rate, thereby allowing the body to more quickly recover.

[0041] To prevent or impede respiratory gases from flowing to the lungs, a variety of impeding or preventing mechanisms may be used, including those described in U.S. Patent Nos. 5,551,420; 5,692,498; 6,062,219; 5,730,122; 6,155,257; 6,234,916 and 6,224,562, and in U.S. Patent Application No. 10/224263, filed on August 19, 2002 ("Systems and Methods for Enhancing Blood Circulation", Attorney Docket No. 16354-000115), 10/401,493, filed March 28, 2003 ("Diabetes Treatment Systems and Methods", Attorney Docket No. 16354-000116), 09/966,945, filed September 28, 2001 and 09/967,029, filed September 28, 2001, the complete disclosures of which are herein incorporated by reference. The valve systems may be configured to completely prevent or provide resistance to the inflow of respiratory gases into the patient while the patient inspires. For valve systems that completely prevent

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the flow of respiratory gases, such valves may be configured as pressure responsive valves that open after a threshold negative intrathoracic pressure has been reached.

[0042] For example, the resistance to the inflow of respiratory gases may be set between about 0 cm H2O and about -25 cm H2O and may be variable or fixed. More preferably, the valve system may be configured to open when the negative intrathoracic pressure is in the range from about -2 cmH2O to about -20 cmH2O. When attempting to improve autonomic function, that valve may be set to open at about -2 cm H2O to about -30 cm H2O, and more preferably range from about -3 cm H2O to about -12 cm H2O.

[0043] Although not intended to be limiting, specific kinds of impedance valves that may be used to reduce intracranial and intraocular pressures include those having spring-biased devices, automated/electronic and mechanical means to occlude and open a valve lumen, duck bill valves, ball valves, and other pressure sensitive valve systems capable of opening and closing when subjected to low pressure differentials triggered either by spontaneous breathing and/or external means to manipulate intrathoracic pressure (such as ventilators, phrenic nerve stimulators, an iron lung, and the like).

[0044] In the past, such threshold valve systems have been used to increase the venous preload on the heart and to increase cardiac output, stroke volume and blood pressure because of the augmented effects of the intrathoracic vacuum on the subsequent cardiac contraction. In contrast, the techniques of the invention function by facilitating the removal of blood from the venous side of the brain. Although there may be an increase in blood flow out of the heart to the vital organs (including to the brain) when using such valve systems, the effect of the valve systems on lowering of intracranial pressures was quite unexpected because of the known increase in blood flow to the brain. Remarkably, however, the reduction of venous blood pressures from the brain remains substantial when using the valve systems. Thus, despite the increase in blood flow to the brain, the net effect of the valve system is a decrease in intracranial pressures.

[0045] With the valve system coupled to the person's airway, the negative intrathoracic pressure may be enhanced by inspiring through the valve system. If the person is spontaneously breathing, the person may simply breath through the valve system. If the person is not breathing, artificial inspiration may be induced using a variety of techniques, including electrical stimulation of the diaphragm, a negative pressure ventilator such as a body cuirass or iron lung, or a positive pressure ventilator capable of also generating a

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vacuum between positive pressure ventilations. As one example, at least some of the respiratory muscles, and particularly the inspiratory muscles, may be stimulated to contract in a repeating manner in order to cause the person to inspire through the valve system, thereby increasing the magnitude and prolonging the duration of negative intrathoracic pressure, i.e.,

5   respiratory muscle stimulation increases the duration and degree that the intrathoracic pressure is below or negative with respect to the pressure in the peripheral venous vasculature. Upon contraction of the respiratory muscles, the patient will typically "gasp". These techniques may be performed alone, or in combination with a valve system.

[0046]   Among the respiratory muscles that may be stimulated to contract are the

10 diaphragm, the chest wall muscles, including the intercostal muscles and the abdominal muscles. Specific chest wall muscles that may be stimulated to contract include those that elevate the upper ribs, including the scaleni and sternocleidomastoid muscles, those that act to fix the shoulder girdle, including the trapezii, rhomboidei, and levatores angulorum scapulorum muscles, and those that act to elevate the ribs, including the serrati antici majores,

15 and the pectorales majores and minores as described generally in Leslie A. Geddes, "Electroventilation - A Missed Opportunity?", Biomedical Instrumentation & Technology, July/August 1998, pp. 401-414, the complete disclosure of which is herein incorporated by reference. Of the respiratory muscles, the two hemi diaphragms and intercostal muscles appear to be the greatest contributors to inspiration and expiration. The respiratory muscles

20 may be stimulated to contract in a variety of ways. For example, the diaphragm may be stimulated to contract by supplying electrical current or a magnetic field to various nerves or muscle bundles which when stimulated cause the diaphragm to contract. Similar techniques may be used to stimulate the chest wall muscles to contract. A variety of pulse trains, pulse widths, pulse frequencies and pulse waveforms may be used for stimulation. Further, the

25 electrode location and timing of pulse delivery may be varied. In one particular aspect, an electrical current gradient or a magnetic field is provided to directly or indirectly stimulate the phrenic nerve.

[0047]   To electrically stimulate the inspiratory motor nerves, electrodes are preferably placed on the lateral surface of the neck over the point where the phrenic nerve, on the chest

30 surface just lateral to the lower sternum to deliver current to the phrenic nerves just as they enter the diaphragm, on the upper chest just anterior to the axillae to stimulate the thoracic nerves, in the oral pharyngeal region of the throat, or on the larynx itself. However, it will be appreciated that other electrode sites may be employed. For example, in one embodiment the

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respiratory muscles are stimulated by a transcutaneous electrical impulse delivered along the lower antero-lat margin of the rib cage. In one embodiment, inspiration is induced by stimulating inspiratory muscles using one or more electrodes attached to an endotracheal tube or pharyngeal tube. To stimulate the diaphragm, the phrenic nerve may be stimulated in the

5   neck region near C3-C7, such as between C3, C4 or C5, or where the phrenic nerves enter the diaphragm. Alternative techniques for stimulating diaphragmatic contraction include magnetic field stimulation of the diaphragm or the phrenic nerve. Magnetic field stimulation may also be employed to stimulate the chest wall muscles. Electrical field stimulation of the diaphragm or the chest wall muscles may be accomplished by placing one or more electrodes

10   on the skin, preferably in the vicinity of the neck or the lower rib cage (although other locations may be employed) and then providing an electrical voltage gradient between electrodes that induces transcutaneous current flow to stimulate the respiratory muscles to contract. Still further, subcutaneous electrodes may also be used to stimulate respiratory muscle contraction. Other techniques are described in U.S. Patent No. 6,463,327, the

15   complete disclosure of which is herein incorporated by reference.

[0048] The valve systems may have a fixed actuating pressure or may be variable so that once a desired negative intrathoracic pressure is reached, the resistance to flow may be lessened. Further, the valves of the invention may be configured to be variable, either manually or automatically. The extent to which the resistance to flow is varied may be based

20   on physiological parameters measured by one or more sensors that are associated with the person being treated. As such, the resistance to flow may be varied so that the person's physiological parameters are brought within an acceptable range. If an automated system is used, such sensors may be coupled to a controller which is employed to control one or more mechanisms that vary the resistance or actuating pressure of the inflow valve as generally

25   described in the references that have been incorporated by reference.

[0049] Hence, the valve systems of the invention may also incorporate or be associated with sensors that are used to detect changes in intrathoracic pressures or other physiological parameters. In one aspect, the sensors may be configured to wirelessly transmit their measured signals to a remote receiver that is in communication with a controller. In turn the

30   controller may use the measured signals to vary operation of the valve systems described or incorporated by reference herein. For example, sensors may be used to sense blood pressure, pressures within the heart, intrathoracic pressures, positive end expiratory pressure, respiratory rate, intracranial pressures, intraocular pressures, respiratory flow, oxygen

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delivery, temperature, blood pH, end tidal CO2, tissue CO2, blood oxygen, cardiac output or the like. Signals from these sensors may be wirelessly transmitted to a receiver. This information may then be used by a controller to control the actuating pressure or the resistance of an inflow valve as described in the references incorporated herein by reference.

5   [0050]   The techniques for reducing intracranial pressures may be used in a variety of settings. For example, the techniques may be used in person's who are spontaneously breathing, those who are not breathing but whose hearts are beating, and those in cardiac arrest. In the latter case, the techniques may use some means to create a vacuum intermittently within the thorax during the performance of CPR. This could be by using a

10   valve system or some other type of pressure manipulation system. Further, such systems may be used in other settings as well, including when the person is breathing.

[0051]   Fig. 1 is flow diagram illustrating one method for reducing intracranial or intraocular pressures, as well as for modulating autonomic function. As shown in step 10, the process proceeds by coupling a valve system to the person's airway. Any kind of coupling

15   mechanism may be used, such as by a mouthpiece, an endotracheal tube, a face mask, or the like. Further, any of the valve systems described or incorporated herein by reference may be used. In step 20, the person's negative intrathoracic pressure is repetitively decreased (either artificially or by spontaneous breathing). Examples of techniques to artificially reduce the negative intrathoracic pressure include use of an iron lung cuirass device, a ventilator that is

20   capable of generating negative pressures, a ventilator that is capable of providing high frequency oscillations at a rate of about 200 to about 2000 per minute, a phrenic nerve stimulator, or the like. As the person's negative intrathoracic pressure is repeatedly decreased while the valve system is coupled to the airway, the pressures in the venous vessels that transport blood out of the head are also lowered. In so doing, intracranial and intraocular

25   pressures are reduced. This in turn may produce an autonomic nervous system-modulated decrease in sympathetic tone and a decrease in peripheral arterial resistance.

[0052]   As shown in step 30, various physiological parameters of the person may optionally be measured. Examples of such parameters include respiratory rate, intrathoracic pressure, intertracheal pressure, intracranial pressure, intracranial blood flow, intraocular pressure,

30   blood pressure, heart rate, end tidal CO_2, oxygen saturation, and the like. Further, as shown in step 40, the valve system's actuating threshold level may optionally be varied based on the measured physiological parameters. This may be done to maximize the amount of blood

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drawn out of the brain or simply to monitor the patient's condition to insure that the patient remains stable.

[0053]   Fig. 2 illustrates one embodiment of a facial mask 100 to which is coupled a valve system 200. Mask 100 is configured to be secured to a patient's face so as to cover the mouth and nose. Mask 100 and valve system 200 are examples of one type of equipment that may be used to lower intrathoracic pressures and thereby lower intracranial and intraocular pressures. However, it will be appreciated that other valve systems and other coupling arrangements may be used including, for example, those previously referenced. As such the invention is not intended to be limited to the specific valve system and mask described below.

[0054]   Referring also to Figs. 3-5, valve system 200 will be described in greater detail. Valve system 200 includes a valve housing 202 with a socket 204 into which a ball 206 of a ventilation tube 208 is received. In this way, ventilation tube 208 may rotate about a horizontal axis and pivot relative to a vertical axis. A respiratory source, such as a ventilation bag, may be coupled to tube 208 to assist in ventilation. Disposed in ventilation tube 208 is a filter 210 that is spaced above a duck bill valve 212. A diaphragm holder 214 that holds a diaphragm 216 is held within housing 202. Valve system 200 further includes a patient port 218 that is held in place by a second housing 220. Housing 220 conveniently includes tabs 222 to facilitate coupling of valve system 200 with facial mask 100. Also held within housing 220 is a check valve 224 that comprises a spring 224a, a ring member 224b, and an o-ring 224c. Spring 224a biases ring member 224b against patient port 218. Patient port 218 includes bypass openings 226 that are covered by o-ring 224c of check valve 224 until the pressure in patient port 218 reaches a threshold negative pressure to cause spring 224a to compress.

[0055]   When the patient is actively ventilated, respiratory gases are forced through ventilation tube 208. The gases flow through filter 210, through duck bill valve 212, and forces up diaphragm 214 to permit the gases to exit through port 218. Hence, at any time the patient may be ventilated simply by forcing the respiratory gases through tube 208.

[0056]   During the exhalation phase of a breathing cycle, expired gases flow through port 218 and lift up diaphragm 214. The gases then flow through a passage 227 in ventilation tube 208 where they exit the system through openings 229 (see Fig. 3).

[0057]   During the inhalation phase of a breathing cycle, valve system 200 prevents respiratory gases from flowing into the lungs until a threshold negative intrathoracic pressure

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level is exceeded. When this pressure level is exceeded, check valve 224 is pulled downward as springs 224a are compressed to permit respiratory gases to flow through openings 226 and to the patient's lungs by initially passing through tube 208 and duck bill valve 212. Valve 224 may be set to open when the negative intrathoracic pressure is in the range from about 0

5   cm H_2O to about –25 cm H_2O, and more preferably from about –2 cm H_2O to about –20 cm H_2O when lowering intracranial pressures. To modulate autonomic function, the cracking pressure may be in the range from about -2 cm H_2O to about -30 cm H_2O, and more preferably range from about -3 cm H_2O to about -12 cm H_2O for flow rates of about 30 to about 50 liters per minute. Hence, the magnitude and duration of negative intrathoracic

10 pressure may be enhanced during patient inhalation by use of valve system 200. Once the intrathoracic pressure falls below the threshold, recoil spring 224a again close check valve 224. In this way, pressure within the venous blood vessels that transport blood out of the brain are also lowered. In so doing, more blood is drawn out of the brain to reduce intracranial and intraocular pressures. As a result, sympathetic tone may be decrease

15 resulting in a decrease in peripheral arterial resistance.

[0058]   Any of the valve systems described herein may be incorporated into a treatment system 300 as illustrated in Fig. 6. System 300 may conveniently include facial mask 100 and valve system 200, although any of the valve systems or interfacing mechanisms described herein or the like may be used. Valve system 200 may conveniently be coupled to

20 a controller 310. In turn, controller 310 may be used to control the impedance level of valve system 200 in a manner similar to any of the embodiments described or incorporated herein. The level of impedance may be varied based on measurements of physiological parameters, or using a programmed schedule of changes. System 300 may include a wide variety of sensors and/or measuring devices to measure any of the physiological parameters described

25 herein. These sensors or measuring devices may be integrated within or coupled to valve system 200 or facial mask, or may be separate.

[0059]   For example, valve system 200 may include a pressure transducer for taking pressure measurements (such as intrathoracic pressures, intracranial pressures, intraocular pressures), a flow rate measuring device for measuring the flow rate of air into or out of the

30 lungs, or a CO_2 sensor for measuring expired CO_2.

[0060]   Examples of other sensors or measuring devices include a heart rate sensor 330, a blood pressure sensor 340, and a temperature sensor 350. These sensors may also be coupled

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to controller 310 so that measurements may be recorded. Further, it will be appreciated that other types of measuring devices may be used to measure various physiological parameters, such as oxygen saturation and/or blood levels of O2, blood lactate, blood pH, tissue lactate, tissue pH, blood pressure, pressures within the heart, intrathoracic pressures, positive end

5   expiratory pressure, respiratory rate, intracranial pressures, intraocular pressures, respiratory flow, oxygen delivery, temperature, end tidal CO2, tissue CO2, cardiac output or the like.

[0061]   In some cases, controller 310 may be used to control valve system 200, to control any sensors or measuring devices, to record measurements, and to perform any comparisons. Alternatively, a set of computers and/or controllers may be used in combination to perform

10   such tasks. This equipment may have appropriate processors, display screens, input and output devices, entry devices, memory or databases, software, and the like needed to operate system 300.

[0062]   A variety of devices may also be coupled to controller 310 to cause the person to artificially inspire. For example, such devices may comprise a ventilator 360, an iron lung

15   cuirass device 370 or a phrenic nerve stimulator 380. Ventilator 360 may be configured to create a negative intrathoracic pressure within the person, or may be a high frequency ventilator capable of generating oscillations at about 200 to about 2000 per minute.

[0063]   Example 1

[0064]   The following is a non-limiting example illustrating how intracranial pressures may

20   be lowered according to the invention. In this example, 30 kg pigs were anesthetized with propofol. Using a micromannometer-tipped electronic Millar catheter inserted below the dura, intracranial pressures were measured continuously in the spontaneously breathing pigs. Intrathoracic pressures (ITP) were recorded using a Millar catheter placed in the trachea at the level of the carina. After stabilizing the pigs blood pressure, heart rate, and ventilation

25   rate, intracranial pressures (ICP) and intrathoracic pressures were recorded, with 0 cmH2O inspiratory impedance and then with inspiratory impedances of 5,10,15, and 20 cm H2O. Inspiratory impedance was achieved using an impedance threshold valve (ITV) as described in Figs. 2-5.

[0065]   At base, the intracranial pressure was approximately 8/4 mmHg. With increasing

30   amounts of inspiratory impedance, the intracranial pressure was lowered proportionally as shown in Figure 7. The intracranial pressure was 6/-2 mmHg when the pig breathed through an impedance of 20 cm H2O. These findings were observed in multiple pig studies and were

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reproducible. Next, the Millar catheter was inserted 3 cm into the pig's brain. The intracranial pressure increased secondary to the trauma associated with the insertion of the probe. The intracranial pressure increased to 25/22 mmHg at the new baseline. Next, the impedance threshold valve was evaluated at different levels of resistance (Fig. 8). Again, there was a decrease in intracranial pressure proportional to the degree of inspiratory impedance.

[0066]   Example 2

[0067]   In this example, intracranial pressures were increased in the setting of recovery from cardiac arrest. The example used a pig model with ventricular fibrillation for 6 minutes followed by cardiopulmonary resuscitation for 6 minutes, followed by defibrillation. Spontaneous breathing resulted in an up to 50% decrease in intracranial pressures when the animals breathed through an inspiratory impedance of 10 cm H2O using a valve system similar to Example 1.

[0068]   In all examples above, the intrathoracic pressure decreased relative to the rest of the body, creating a suction effect that reduced the pressure in the venous blood vessels draining the brain, thereby reducing intracranial pressures.

[0069]   The invention further provides techniques and devices for reducing intracranial pressure (ICP) by facilitating movement of cerebral spinal fluid (CFS). There are a number of causes of increased ICP including: head injury, ischemia, osmolar imbalance, cerebral edema, tumors, complications of dialysis, infections, stroke, hypertensive crises. Each can result in a slow, and in some cases, an acute rise in the ICP. The solid matter of the brain contents makes up about 80-85% of the material enclosed by the skull. Cerebral blood volume accounts for 3-6% and CSF for 5-15%. See, Anesthesia, Third Edition Editor, Ron Miller. Chapter authors: Shapiro and Drummond. Chapter 54 (1990), the complete disclosure of which is herein incorporated by reference. CSF moves within the brain from its site of production to its site of reabsorption in the brain in an unimpeded manner under normal physiological states. Since the contents in the brain are practically incompressible, a change in volume of any one of the three major components (brain matter, blood volume, CSF volume) results in a reciprocal change in one or both of the other brain components. When the volume of the brain expands, secondary to an increase in the non-CSF component(s), some of the CSF is forced to other locations, including through the foramen magnum (hole in skull connecting skull to space where the spinal cord is located) and into the CSF fluid space

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surrounding the spinal cord. When the non-CSF components expand in volume or size, the intracranial pressure rises. Normal ICP levels are 10-15 mmHg when supine. At levels greater than 15-20 mmHg, damage to the brain can occur secondary to compression and resultant tissue ischemia (lack of adequate blood flow). A reduction in ICP levels can be

5 achieved by a number of clinical interventions including water restriction, diuretics, steroids, hyperventilation, a reduction of cerebral venous pressure, hypothermia, CSF drainage, and surgical decompression.

[0070] Increased ICP results in reduced CSF fluid movement and translocation. CSF fluid production generally remains constant (about 150 ml/day) despite elevated ICP. CSF fluid

10 reabsorption is can be slowed by elevated ICP. By using the valve systems described herein, central venous pressures may be reduced. In turn, this results in a decrease in ICP and results in an increase in CSF fluid movement or translocation and reabsorption. This results in a further reduction in ICP.

[0071] The valve systems of the invention may be used in spontaneously breathing

15 individuals, in patients ventilated with negative pressure ventilation or in patients ventilated with a ventilator that causes a decrease in central venous pressures for at least a portion of the respiratory cycle. Each time the intrathoracic pressure is reduced with the valve systems of the invention, there is a concomitant reduction in ICP and an increase in the movement of CSF. In other words, there is an increase in the difference between the peak and trough of the

20 ICP wave form when using the valve systems. The sinusoidal movement occurs in spontaneously breathing people because of the change in pressure in the thorax that is transmitted to the brain via the venous blood vessels. The normally fluctuating CSF pressures (the pressure increases and decreases with each inspiration) are altered by the valve systems. More specifically, the valve systems create a lower trough value thereby creating an

25 overall created change in the ICP with each inspiration. In the non-breathing patient, a similar effect can be produced with the valve systems when used with a variety of ventilator devices, including an iron lung, a phrenic nerve stimulator (such as those described in U.S. Patent Nos. 6234985; 6224562; and 6312399, incorporated herein by reference), a suction cup on the chest that is used to periodically expand the chest and the like.

30 [0072] Increased CSF fluid movement results in an overall improved metabolic state for the brain. This is shown schematically in Figs. 9A and 9B. In Fig. 9A, the brain 400 is shown under normal conditions. The brain 400 is surrounded by CSF 402 which is produced at a

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site 404. The CFS in turn is surrounded by the skull 406. Blood enters brain 400 through an artery 408 and exits through a vein 410. Vein 410 also includes a site 412 of CFS drainage. Shown in Fig. 9A is an arrow showing the direction of CFS flow when draining. Extending from brain 400 is the spinal cord 414 that is surrounded by the foramen magnum 416.

5   [0073]   In Fig. 9B, the brain 400 is significantly swollen which reduces the space 402 where the CFS is located. The swelling of the brain 400 can cause blockage of CSF to the spinal cord 414 as shown by arrow 418. Also, movement of CSF to site 412 is reduced to hinder movement of CSF out of the skull 406.

[0074]   By treating the elevated ICP associated with all of the conditions noted above using
10   the valve systems described herein, brain swelling can be reduced. In so doing, CFS movement and fluid translocation is increased under those same conditions. This results in a further decrease in intracranial pressure as the CSF is able to relocate.

[0075]   Referring now to Fig. 10, the effects of contracting the atria of the heart on ICP will be described. As shown, contraction of the atria results in a phasic movement in ICP. This
15   can be most clearly demonstrated during cardiac ventricular fibrillation. In that setting, the atria often beat spontaneously and the pressure of each contraction and relaxation waveform is transmitted immediately to the brain and is reflected in nearly identical fluctuations in ICP. The inventor has discovered that the fluid systems (venous blood vessels and CSF) are so closely linked, that subtle changes in the heart rhythm result in immediate changes in CSF
20   pressure. Thus, in some patients with significant heart rhythms, or significant heart failure, the rise in right heart pressures as a result of these conditions results in an increase in ICP. Such rises in ICP can lead to a decrease in cerebral perfusion, since cerebral perfusion is determined by the pressure of the blood entering the brain (mean arterial pressure) minus the pressure of the blood leaving the brain (ICP and central venous pressure). Use of the valve
25   and intrathoracic vacuum systems described herein will result in a decrease in intrathoracic pressure. As shown in Fig. 10, the downwardly pointing arrows represent the timing of each inhalation through the valve system. In the baseline state, before the onset of atrial fibrillation, each inspiration (small arrows) results in a reduction in ITP, a reduction of right atria pressure, a reduction in central venous pressures, and then an immediate reduction in
30   ICP. With the onset of atrial fibrillation, the intracranial pressure rises and the sinusoidal pattern of ICP amplitude changes becomes dampened. As soon as the animal begins to inspire through an inspiration impedance of -10 cm H20 there is an immediate decrease in intrathoracic pressure (ITP), an immediate decrease in right atrial (RA) pressures , and an

immediate decrease in intracranial pressure (ICP) along with the restoration of a sinusoidal fluctuation in ICP with each inspiration. With elevated ICP, inspiration through the impeding means results in a decrease in ICP, increased cerebral spinal fluid flow, and a decrease in cerebral ischemia secondary to increased cerebral perfusion. As such, the valve systems can used in patients with heart rhythms, such as atrial fibrillation, or patients with heart failure who have increased ICP in order to reduce their ICP, increase CSF fluid movement and translocation, and ultimately help them to improve their brain function.

[0076] Hence, the amount of inspiratory resistance, or the amount of negative intrathoracic pressure generation (which may be generated using a variety of techniques) can be controlled or regulated by feedback from measurement of ICP, blood pressure, respiratory rate, or other physiological parameters. Such a system could include a closed loop feedback system.

[0077] Fig. 11 is a flow chart illustrating another method for treating a person suffering from head trauma associated with elevated intracranial pressures. In so doing, it will be appreciated that such techniques may also be used to treat those suffering from low blood pressure or those in cardiac arrest, among others. The techniques are particularly useful in cases where the person is not breathing, although in some cases they could be used for breathing patients as well.

[0078] In a broad sense, when treating a person suffering from head trauma, a person's intrathoracic pressure is lowered to decrease intracranial pressures. In turn, this assists in reducing secondary brain injury. As shown in step 500, equipment may be coupled to the person to assist in lowering the person's intrathoracic pressure. A wide variety of equipment and techniques may be used to decrease the intrathoracic pressure, including using a mechanical ventilator capable of extracting respiratory gases, such as the one described in U.S. Patent No. 6,584,973, a phrenic nerve or other muscle stimulator (with or without the use of an impedance mechanism, such as those described in U.S. Patent Nos. 5,551,420; 5,692,498; 6,062,219; 5,730,122; 6,155,257; 6,234,916 and 6,224,562) such as those described in U.S. Patent Nos. 6234985; 6224562; 6312399; and 6463327, an iron lung device, a thoracic vest capable of pulling outward on the chest wall to create an intrathoracic vacuum similar to the effect of an iron lung, a ventilatory bag, such as the one described in copending U.S. Application No. 10/660,366, filed 09/11/2003 (attorney docket no. 16354-005400), filed on the same date as the present application, and the like. The complete disclosures of all these references are herein incorporated by reference. For breathing

patients, a threshold valve as described above and that is set to open when about 5 cmH20 is generated during an inhalation may be used to enhance the person's negative intrathoracic pressure.

[0079] When the person is not breathing, a positive pressure breath is delivered to the person as illustrated in step 502. This may be done with a mechanical ventilator, a ventilatory bag, mouth to mouth, and the like. This is followed by an immediate decrease in intrathoracic pressure. This may be done by extracting or expelling respiratory gases from the patient's lungs as shown in step 504. Any of the techniques described above may be used to lower the intrathoracic pressure. Such a reduction in intrathoracic pressure also lowers central venous pressure and intracranial pressure.

[0080] The vacuum effect during the expiratory phase may be constant, varied over time or pulsed. Examples of different ways to apply the vacuum are described later with respect to Figs. 12A-12C. The initial positive pressure breath may be supplied for a time of about 250 milliseconds to about 2 seconds, and more preferably from about 0.75 seconds to about 1.5 seconds. The respiratory gases may be extracted for a time that is about 0.5 to about 0.1 to that of the positive pressure breath. The positive pressure breath may be delivered at a flow rate in the range from about 0.1 liters per second to about 5 liters per second, and more preferably from about 0.2 liters per second to about 2 liters per second. The expiratory flow (such as when using a mechanical ventilator) may be in the range from about 0.1 liters per second to about 5 liters per second, and more preferably from about 0.2 liters per second to about 2 liters per second. The vacuum may be maintained with a negative flow or without any flow. The vacuum may be in the range from about 0 mmHg to about -50 mmHg, and more preferably from about 0 mmHg to about -20 mmHg.

[0081] As shown in step 506, the process of delivering a positive pressure breath and then immediately lowering intrathoracic pressures may be repeated as long as necessary to control intracranial pressures. Once finished, the process ends at step 508.

[0082] The manner in which positive pressure breaths and the vacuum are created may vary depending upon a particular application. These may be applied in a variety of waveforms having different durations and slopes. Examples include using a square wave, biphasic (where a vacuum is created followed by positive pressure, decay (where a vacuum is created and then permitted to decay), and the like. Three specific examples of how this may occur are illustrated in Figs. 12A-12C, although others are possible. For convenience of discussion,

the time during which the positive pressure breath occurs may be defined in terms of the inspiratory phase, and the time during which the intrathoracic pressure is lowered may be defined in terms of the expiratory phase. The positive pressure breaths may occur at about 10 to about 16 breaths per minute, with the inspiratory phase lasing about 1.0 to about 1.5 seconds, and the expiration phase lasing about 3 to about 5 seconds. As shown in Fig. 12A, respiratory gases are quickly supplied up to a pressure of about 22 mmHg. This is immediately reversed to a negative pressure of about -10 mmHg. This pressure is kept relatively constant until the end of the expiratory phase where the cycle is repeated.

[0083] In Fig. 12B, the positive pressure is more slowly applied. When reaching a pressure of about 10 to about 15 mmHg, the pressure is rapidly reversed to a negative pressure of about -20 mmHg. The negative pressure gradually declines to about 0 mmHg at the end of the expiratory phase. The cycle is then repeated. Hence, in the cycle of Fig. 12B, the positive pressure is reduced compared to the cycle in Fig. 12A, and the negative pressure is initially lower, but allowed to gradually increase. The technique is designed to help reduce a possible airway collapse.

[0084] In Fig. 12C, the positive pressure is brought up to about 20 mmHg and then immediately brought down to about 0 mmHg. The negative pressure is then gradually increased to about -20 mmHg toward the end of the expiratory phase. This cycle is designed to help reduce a possible airway collapse.

[0085]   The following examples illustrate the effectiveness of a threshold valve system to modulate autonomic function. In Examples 3-5, a threshold valve system (also referred to as an inspiratory impedance threshold device) similar to the ones described herein (see Figs. 2-5) is interfaced to an airway.

[0086] Example 3

[0087] In this example, blood pressure changes and survival rate are evaluated in severe hemorrhagic shock treated with an inspiratory impedance threshold device (ITD) set to prevent inspiratory airflow until the intratracheal pressure falls below -10 cm H_2O without affecting expiration.

[0088] Design: Randomized.

[0089] Setting: University animal laboratory.

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[0090]   Subjects: Yorkshire-cross pigs (22-31 kg).

[0091]   Intervention: Controlled bleeding of 50% of calculated blood volume followed by treatment with an ITD or observation for 90 minutes. Prior to bleeding, all the animals were intubated and anesthetized but allowed to spontaneously breathe. After 90 minutes of treatment, saline was administered and the animals were allowed to recover.

[0092]   Measurements and main results: Systolic blood pressure after ten minutes of treatment with the ITD was higher in the treatment group than in the control group (70.3 ± 5.8 vs. 50.1 ± 3.1 mmHg respectively, $P<0.01$). All of the pigs in the control group died within 65 min whereas 7/8 (87%) treated with an ITD survived for 90 minutes ($P<0.001$). During the recovery phase, one animal in the treatment group never woke up from anesthesia and 6/8 (75%) survived past 3 hours. No focal neurological defects were found after recovery. Treatment with the ITD was not associated with hypoxia.

[0093]   Conclusion: ITD treatment during hemorrhagic shock improved blood pressure and increased survival rates in spontaneously breathing pigs.

[0094]   Example 4

[0095]   Objective: An inspiratory impedance threshold device (ITD) was evaluated in spontaneously breathing animals with hypotension to determine if it could help improve systemic arterial pressures when fluid replacement was not immediately available.

[0096]   Design: Prospective, randomized

[0097]   Setting: Animal laboratory

[0098]   Subjects: Female farm pigs (wt 28-33 kg)

[0099]   Interventions: Anesthetized spontaneously breathing pigs were treated with an ITD, with cracking pressures from 0 to –20 cmH_2O. Four separate experiments were performed:

[0100]   A. Initial studies in normotensive and hypovolemic hypotensive pigs (n=7) focused on the effects of 4 different ITD cracking pressures (-5,-10, -15, -20 cm H_2O) on hemodynamic variables;

[0101]   B. Pigs were hemorrhaged to a systolic blood pressure (SBP) of 50-55 mmHg, and then treated with a sham (n=9) or active ITD (-12 cmH_2O) (n=9);

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[0102] C. The effect of the ITD (-12 cmH$_2$O) on arterial and mixed venous gases was evaluated in hypotensive hypovolemic pigs (n=7);

[0103] D. Cardiac output was measured in hypotensive hypovolemic pigs (n=7) by thermodilution before and after treatment with the ITD (-12 cmH$_2$O) (n=9).

[0104] Methods and Main Results: During initial studies with both normovolemic and hypovolemic pigs, sequential increases in inspiratory impedance resulted in a significant increase in SBP; whereas diastolic left ventricular (dLV) and right atrial (dRA) pressures decreased significantly and proportionally to the level of impedance. When comparing the sham versus active ITD (-12 cmH$_2$O) in hypotensive pigs, SBP (mean ± SEM) with active ITD treatment rose from 70 ± 2 mmHg to 105 ± 4 mmHg (p<0.01). Pressures in the control group remained at 70 ± 4 mmHg (p<0.01). Heart rates in the animals treated with the active ITD (160 ± 2 bpm) were significantly lower than in the controls (169±-3 bpm)(p<0.02). Cardiac output increased by nearly 25% (p<0.01) with the active ITD when calculated using the mixed gas equation and when determined by thermodilution.

[0105] Conclusions: These studies demonstrate that it is feasible to use a device that creates inspiratory impedance in spontaneously breathing normotensive and hypotensive pigs to increase blood pressure and enhance cardiopulmonary circulation in the absence of immediate fluid resuscitation.

[0106] Example 5

[0107] Increased negative intrathoracic pressure during spontaneous inspiration through an impedance threshold device (ITD) causes an elevation in systemic arterial blood pressure in humans. The hypothesis was that the acute increase in blood pressure induced by breathing through an ITD would be associated with increased stroke volume (SV) and cardiac output (CO). This hypothesis was tested by measuring hemodynamic and respiratory responses in 10 female and 10 male subjects during two separate ITD conditions: (a) breathing through a face mask with an ITD set at approximately 6 cm H$_2$O; and, (b) breathing through the same face mask with a sham ITD (control). The duration of ITD breathing was 14 min. The order of the two experimental conditions was counterbalanced, and each experiment was performed on a separate day. SV was measured by thoracic bioimpedance. All hemodynamic measurements were repeated 5 min after cessation of ITD breathing. Compared with the control (sham) condition, ITD produced higher SV (124 ± 3 vs 137 ± 3 ml, P = 0.013), HR (63 ± 3 vs 68 ± 3 ml, P = 0.049), CO (7.69 vs 9.34 liters/min, P = 0.001), and SBP (115 ± 2

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to 122 ± 2 mmHg, P = 0.005) without affecting expired minute ventilation volume (6.2 ± 0.4 to 6.5 $\pm$ 0.4 liters/min, P = 0.609). There were no gender effects and all hemodynamic responses returned to control (sham) levels by 5 min after cessation of ITD breathing.

[0108] Conclusions: ITD breathing at relatively low impedance can increase arterial blood pressure in otherwise healthy subjects by increasing SV and CO. The ITD may therefore provide short-term protection against cardiovascular collapse induced by orthostatic stress or hemorrhage.

[0109] The invention has now been described in detail for purposes of clarity and understanding. However, it will be appreciated that certain changes and modifications may be practiced within the scope of the appended claims.